Health and Social Care

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

Interface Pharmacist Network Specialist Medicines

Azathioprine adult (non-transplant indications)

Shared Care Guideline

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

Licensed indications include:
Crohn's disease, ulcerative colitis, systemic lupus erythematosus, dermatomyositis, polymyositis, autoimmune hepatitis, pemphigus vulgaris, polyarteritis nodosa, auto-immune haemolytic anaemia, chronic refractory idiopathic thrombocytopenic purpura (ITP), severe rheumatoid arthritis.
Unlicensed indications include:
Dermatological indications: atopic dermatitis, bullous pemphigoid, chronic actinic dermatitis, pyoderma gangrenosum, chronic spontaneous urticaria, angioedema, urticarial vasculitis.
Respiratory indications: Non specific interstitial pneumonia; Hypersensitivity pneumonitis, Connective tissue related Interstitial Lung disease, Lymphocytic interstitial pneumonia, Cryptogenic organising pneumonia (COP), Desquamatous interstitial pneumonia (DIP), granulomatous lymphocytic infiltrative lung disease.
Systemic vasculitis of any aetiology eg. granulomatosis with polyangiitis (GPA: formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), giant cell arteritis, Takayasu's arteritis, eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome).
Other: sarcoidosis, Sjogren's syndrome, scleroderma, myasthenia gravis, inflammatory eye disease.

Adult dosage and administration

Dosage regimens may vary between 0.5 – 3 mg/kg daily specific to the patient and the condition.
Dosage may need to be reduced in patients with renal and/or mild to moderate hepatic impairment.
Available as:
- Azathioprine 25mg, 50mg tablets.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with azathioprine.
- Agree shared care with patient's GP.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Advise GP on dose of azathioprine to be prescribed.
- Provide the patient/carer with relevant (preferably written) information on use, side effects and need for monitoring of medication.
- Undertake baseline tests as indicated in the monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.

<table>
<tr><th colspan="2">Monitoring table</th><th>Hospital specialist</th><th colspan="3">GP</th><th>Hospital specialist</th></tr>
<tr><th rowspan="2">Test</th><th rowspan="2">Indication</th><th rowspan="2">Pre-treatment baseline</th><th colspan="3">During treatment</th><th rowspan="2">At review</th></tr>
<tr><th>Until on stable dose for 6 weeks</th><th>Next 3 months</th><th>Thereafter</th></tr>
<tr><td>FBC
LFTs
U&Es, eGFR</td><td>Baseline assessment, dose adjustment</td><td>✓</td><td>Every 2 weeks</td><td>Every month</td><td>Every 3 months</td><td rowspan="2">As part of the review or as clinically indicated</td></tr>
<tr><td>ESR/CRP
(Rheumatology and Gastroenterology only)</td><td>Disease activity scoring</td><td>✓</td><td colspan="3">Every 3 months</td></tr>
<tr><td>Height & weight</td><td>Baseline assessment</td><td>✓</td><td colspan="3" rowspan="4">Not routinely required</td><td rowspan="4">If clinically indicated</td></tr>
<tr><td>Blood pressure
Chest x-ray
PFTs, TB screening if indicated</td><td>Baseline assessment, respiratory and TB screening</td><td>If clinically indicated</td></tr>
<tr><td>Urinalysis</td><td>To assess for renal disease (proteinuria) or infection</td><td rowspan="2">✓</td></tr>
<tr><td>TPMT</td><td>To assess suitability for treatment</td></tr>
<tr><td colspan="2">Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding</td><td>✓</td><td colspan="3">At every consultation</td><td>✓</td></tr>
<tr><td colspan="7">If a further DMARD/JAK is added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated. There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist.</td></tr>
</table>

GP responsibilities

- Prescribe azathioprine.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly eg. asplenia), see BNF or Green Book.
- Provide COVID 19 and **inactivated** shingles (Shingrix®) vaccination as appropriate as per local arrangements and Green Book
- Post exposure prophylaxis (antivirals or VZIG if antivirals are contraindicated) should be considered in non-immune at risk patients if exposed to chickenpox or shingles. Contact the consultant virologists, Regional Virus Laboratory, Royal Group of Hospitals on 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals
- Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding at every consultation.

Withhold azathioprine and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia > 0.5 x 10^9/L
- Platelets < 120 x 10^9/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 - 3 x ULN, continue azathioprine, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common
- If renal impairment develops (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough.

Normal reference range may vary slightly between labs.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

General signs of malaise such as dizziness, diarrhoea, rash, myalgia and arthralgia occur infrequently. If severe or persistent refer to initiating specialist.
Renal impairment. Caution is advised regarding adequacy of renal function if azathioprine is to be used concomitantly with NSAIDs, ACE inhibitors or angiotensin II antagonists.
Infection. Immunosuppressants can increase susceptibility to infection. It is advisable not to commence or continue treatment with azathioprine when patients have a confirmed or established local or systemic infection. It is advisable to recommence once the infection has been treated. Precise period of discontinuation depends on the nature and severity of infection and the activity of the underlying disease.
Nausea can occur initially but can be reduced by taking the tablets after food.
Blood disorders: leucopenia, anaemia and thrombocytopenia. GPs should be alert to any oral ulceration, sore throat, unexplained rash or abnormal bruising/bleeding.
Pancreatitis has been reported in a small percentage of patients.
Pregnancy / contraception. Women of childbearing potential and men receiving azathioprine should be advised to use effective contraception. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without discontinuing azathioprine.
Breastfeeding. Women being treated with azathioprine should seek specialist advice.
Cancer risk. Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.
Contraindications include:

- Hypersensitivity to mercaptopurine
- Severe hepatic impairment
- TPMT deficiency - avoid if deficient or reduce dose if low levels.

Common drug interactions

Allopurinol prolongs activity of azathioprine increasing risk of severe myelosuppression. If it must be given concomitantly, it is essential that only a quarter of the usual dose of azathioprine is given.
Aminosalicylates (eg. sulfasalazine) contribute to bone marrow toxicity and increased monitoring may be required. A lower dose of azathioprine may be required.
Concomitant use of **ACE inhibitors** are predicted to increase risk of anaemia/leucopenia. Increased monitoring may be required.
JAK inhibitors may enhance the immunosuppressive effects of azathioprine. Concomitant use of filgotinib should be avoided; baricitinib should be used cautiously in combination.
Febuxostat: avoid concomitant use.
Ribavarin: increases risk of myelosuppression.
Trimethoprim and co-trimoxazole: there is a risk of haematological abnormalities.
Warfarin effect may be reduced requiring an increased dose of warfarin.

Communication

For any queries relating to this patient's treatment with azathioprine, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC at www.medicines.org.uk or the BNF

Date prepared: June 2023 Date of review: June 2028